# Quantitative Evaluation of Initial Symptoms as Predictors to Detect Adverse Drug Reactions Using Bayes' Theory: Expansion and Evaluation of Drug-Adverse Drug Reaction–Initial Symptom Combinations Using Adverse Event Reporting System Database

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**In prescription dispensing in Japan, to avoid adverse drug reactions (ADR) pharmacists provide patients with information concerning the initial symptoms (IS) of any ADR that might be caused by the drugs they have been prescribed. However, the usefulness of such information for preventing ADR has not been quantitatively evaluated. We previously performed a trial calculation of the usefulness of rash as a predictor of drug-induced liver disorders by applying Bayes' theorem and showed that the predictive utility of IS can be quantitatively evaluated using likelihood ratios. However, for other drug-ADR-IS combinations it was difficult to obtain the information required for the calculations from Japanese data alone. In this study, using the Adverse Event Reporting System (AERS) database of the U.S. Food and Drug Administration (FDA), we evaluated 132 drug-ADR-IS combinations that were considered to be potentially clinical significant. Regarding bezafibrate-associated rhabdomyolysis and cibenzoline-associated hypoglycemia, these ADR were not detected in cases involving monotherapy. For 58 combinations, no events that were considered to be IS of the target ADR developed. Fever, nausea, and decreased appetite were the IS of many ADR, making them very useful predictors. In contrast, pruritus and rash were not very useful. Fever might be a predictor of thiamazole-induced agranulocytosis or levofloxacin- or terbinafine-induced liver disorder, tremors might be useful for predicting paroxetine-induced serotonin syndrome, and decreased appetite might be a useful indicator of terbinafine-induced liver dysfunction.**

**Key words** Bayes' theory; initial symptom; Adverse Event Reporting System; adverse drug reaction; information service

In Japan, when pharmacists dispense drugs to patients they provide information about any symptoms that the prescribed medication might induce that should cause the patient to consult a physician in order to avoid adverse drug reactions (ADR). Specifically, article 25-2 of the Pharmacists Act (1997) obliges pharmacists to describe to patients the initial symptoms (IS) of any ADR that might be induced by the drugs they have been prescribed.

Since the information provided about the IS of ADR has to be easy for patients to understand, less specific symptoms, mainly changes in their physical condition, such as fever, rash, or muscular pain, are described. However, it is doubtful whether such information is useful for detecting ADR.

In our previous report, we performed a trial calculation of the usefulness of rash as an IS of liver disorder; *i.e.*, as an ADR predictor, using Bayes' theorem.[1)] For voriconazole, the prior probability of liver disorder, 0.05, was increased to 0.2 when a rash was present, whereas liver disorders only developed in 2 of 1000 patients who developed a rash after taking loxoprofen sodium, showing that the value of an IS as a predictor varies depending on the drug being taken.

Bayes' theorem is widely used to evaluate the predictability of a single or a combination of multiple diagnoses.[2)] However, to use Bayes' theorem to assess the utility of IS of ADR as diagnostic predictors, it is necessary to identify the probability of a specific symptom accompanying a particular ADR, and we were only able to determine these probabilities for a small number of drugs using Japanese data in our previous study.

The Adverse Event Reporting System (AERS) database, which is run by the U.S. Food and Drug Administration (FDA), contains over four million reports of adverse events (AE). It relies on reports of spontaneous adverse events being submitted to the FDA by health professionals, consumers, and manufacturers. In this study, we used this database in order to markedly increase the number of drug-ADR-IS combinations involving commonly used drugs for which the above mentioned calculations could be performed. In addition, the results of the calculations provided us with some interesting insights.

## THEORY

**Calculation of Posterior Probability** When an IS (I) that is considered to be a predictor of a particular ADR (A) develops after a certain drug (D) is taken, the probability of A actually developing ($P_{post}$) is given by the equation below:

$$P_{post} = \frac{P_{pre}(Q_{pre} + Q_{non})}{P_{pre}(Q_{pre} + Q_{non}) + P_{other}(Q_{other} + Q_{non}) + P_{non}Q_{non}} \quad (1)$$

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$$P_{post} = \frac{P_{pre}(Q_{pre} + Q_{non})}{P_{pre}Q_{pre} + P_{other}Q_{other} + Q_{non}(P_{pre} + P_{other} + P_{non})} = \frac{P_{pre}(Q_{pre} + Q_{non})}{Q_t - P_{non}Q_{non} + Q_{non}} \quad (2)$$

where: $P_{post}$: Incidence of A accompanied by I, $P_{pre}$: Incidence of A, $P_{other}$: Incidence of ADR other than A, $P_{non}$: Probability of no ADR developing, $Q_{pre}$: Probability of D-induced I accompanying A, $Q_{other}$: Probability of D-induced I accompanying an ADR other than A, $Q_{non}$: Incidence of I-like symptoms that are not drug-related, $Q_t$: Total incidence of D-induced I in clinical trials

$$Q_t = P_{pre}Q_{pre} + P_{other}Q_{other} + P_{non}Q_{non}$$

The addition of $Q_{non}$ to $Q_{pre}$ and $Q_{other}$ in Eq. 1 assumes that the incidence of I-like symptoms that are not drug-related is not included in $Q_{pre}$ or $Q_{other}$. ADR are defined as reactions for which an association with a particular drug cannot be ruled out, and IS are mild ADR. Accordingly, it can be assumed that $Q_{non}$ is not included in $Q_{pre}$ or $Q_{other}$.

$Q_{pre}$ and $Q_{other}$ were calculated using the AERS data. Since the AERS data are comprised of AE reports, $Q_{pre}$ and $Q_{other}$ were considered to include $Q_{non}$. However, since we calculated $Q_{pre}$ and $Q_{other}$ from the data of drugs used alone. Therefore, it is strongly assumed that reporters of AE considered the drug to be the primary suspect and reported the event as an ADR. Thus, in the calculation of $P_{post}$, we made 2 calculations: $Q_{non}$ was added to $Q_{pre}$ and $Q_{other}$ in one (*CalQ+*) and not added in the other (*CalQ0*), broadening the range of interpretation of the results. The $P_{post}$ values produced using *CalQ+* and *CalQ0* are presented as $P_{post}Q+$ and $P_{post}Q0$, respectively.

Equation 2 is only applicable when the total number of individuals who took a particular medication is known, as the latter figure is required $Q_t$. Since the AERS data did not describe the number of patients who took each drug without developing AE, we did not use Eq. 2 in this study.

**Calculation of Likelihood Ratios** The positive likelihood ratio was calculated using Eq. 3.

$$LR+ = \frac{Od_{post}}{Od_{pre}} = \frac{P_{post}(1-P_{pre})}{P_{pre}(1-P_{post})} \quad (3)$$

where: *LR+*: Likelihood ratio, $Od_{pre}$: Prior odds, $Od_{post}$: Posterior odds

*LR+* values that were calculated using $P_{post}Q+$ and $P_{post}Q0$ as $P_{post}$ were designated as *LR+Q+*and *LR+Q0*, respectively.

## METHODS

**Incidence of IS-Like Symptoms That Were Not Caused by the Target Drug ($Q_{non}$)** The IS of ADR, such as fever, headache, and muscular pain, are also experienced as changes in physical condition that are not caused by drugs in daily life. Of these changes in physical condition, those that occur without an obvious cause, such as a cold or excess exercise, need to be differentiated from the IS of ADR, and knowledge about their incidence is required to calculate the frequency of non-specific background IS-like symptoms; *i.e.*, $Q_{non}$ in Eq. 1. Thus, we first investigated $Q_{non}$.

**Selection of IS for the $Q_{non}$ Investigation** The examined IS were selected from "the Manual for Handling Disorders due to Adverse Drug Reactions" (MHD).[3] The MHD was published by the Ministry of Health, Labour, and Welfare and was produced in cooperation with academics in order to develop a strategy for dealing with disorders caused by ADR. In particular, the MHD aims to prevent severe ADR being overlooked during their early stages.[4] So, we selected IS that exhibited high incidences from the MHD for our investigation of $Q_{non}$.

**Survey of $Q_{non}$** $Q_{non}$ was investigated using an internet-based questionnaire developed by Rakuten Research (Rakuten Research, Inc., Shinagawa, Tokyo, Japan). Nine hundred males and 900 females belonging to 6 decile age groups, ranging from subjects in their 20s to patients in their 70s (150 males and 150 females in each age group), were surveyed about any changes in their physical condition of unknown cause that had occurred during the last 3 months. The survey period was set at 3 months because many ADR develop within 3 months of the initiation of drug treatment.[5] We have reported the findings of this survey previously.[1] The results are shown together with the incidence of urticaria-like changes in physical condition in Table 1.

**Selection of Drug-ADR-IS Combinations** On the condition that one of the target IS examined in the investigation of $Q_{non}$ was included in each combination, 3 pharmacists selected drug-ADR-IS combinations from the MHD from the viewpoint of clinical importance about patient compliance instruction. That is, the process used to select the drug-ADR-IS combinations was as follows: First, IS that were frequently mentioned in the MHD were extracted. Then, we identified ADR involving these IS. Finally, we extracted drugs associated with these ADR.

The terms used to describe the ADR and IS were standardized to the Preferred Terms outlined in the Japanese edition of the ICH Medical Dictionary for Regulatory Activities Terminology (MedDR/J).

**Data Collection. $P_{pre}$, $P_{other}$, and $P_{non}$** The probabilities of the target ADR ($P_{pre}$), ADR other than the target ($P_{other}$), and no ADR developing ($P_{non}$) were adopted from the "ADR frequencies classified by item and a list of abnormal clinical laboratory test results" (a list of ADR) section of the post-marketing surveillance (PMS) data on each drug's interview form (IF). The IF of brand name drugs were used.

**$Q_{pre}$ and $Q_{other}$** Using the AERS data, the total number of cases of ADR, the number of cases of the target ADR, and the number of cases of the target ADR that were accompanied by the target IS were investigated for each drug used alone, and $Q_{pre}$ and $Q_{other}$ were determined.

**Statistical Analysis** The difference between $P_{pre}$ and $P_{post}$ was analyzed arbitrarily by setting the population size to that of the PMS.

## RESULTS

**Drug-ADR–IS (D-A-I) Combinations and the Results of the AERS Survey** The target D-A-I combinations are shown in Table 2. "★" represents IS that were not found in the AERS database.

Regarding bezafibrate-associatefd rhabdomyolysis and cibenzoline-associated hypoglycemia, the ADR were not induced by these drugs alone. Therefore, they have been marked with "★★."

Table 1. Incidence Rates of Changes in Body Condition

| ID | Symptom | Incidence | ID | Symptom | Incidence |
|---|---|---|---|---|---|
| 1 | Fatigue | 0.1644 | 27 | Increased blood pressure | 0.0494 |
| 2 | Pruritus | 0.1450 | 28 | Dry cough | 0.0494 |
| 3 | Malaise | 0.1339 | 29 | Edema | 0.0439 |
| 4 | Headache | 0.1250 | 30 | Nausea | 0.0428 |
| 5 | Diarrhea | 0.1161 | 31 | Anemia | 0.0417 |
| 6 | Arthralgia | 0.1139 | 32 | Musculoskeletal stiffness | 0.0411 |
| 7 | Tinnitus | 0.1000 | 33 | Hyperhidrosis | 0.0406 |
| 8 | Abdominal distensiom | 0.0961 | 34 | Erythema | 0.0389 |
| 9 | Constipation | 0.0883 | 35 | Wet cough | 0.0389 |
| 10 | Somnolence | 0.0872 | 36 | Decreased appetite | 0.0378 |
| 11 | Dizziness | 0.0861 | 37 | Pyrexia | 0.0350 |
| 12 | Rash | 0.0833 | 38 | Facial edema | 0.0294 |
| 13 | Insomnia | 0.0800 | 39 | Tachycardia | 0.0289 |
| 14 | Pollakiuria | 0.0783 | 40 | Dysponea | 0.0250 |
| 15 | Oropharyngeal pain | 0.0783 | 41 | Bruising | 0.0239 |
| 16 | Abdominal pain | 0.0761 | 42 | Black stools | 0.0228 |
| 17 | Abdominal discomfort | 0.0700 | 43 | Dyslalia | 0.0206 |
| 18 | Urticaria | 0.0614 | 44 | Asthenia | 0.0200 |
| 19 | Palpitations | 0.0606 | 45 | Tremors | 0.0194 |
| 20 | Muscle ache | 0.0572 | 46 | Oliguria | 0.0189 |
| 21 | Epigastrial pain | 0.0561 | 47 | Vomiting | 0.0189 |
| 22 | Hemorrhage(*) | 0.0556 | 48 | Wheezing | 0.0161 |
| 23 | Thirst | 0.0544 | 49 | Ageusia | 0.0150 |
| 24 | Heart burn | 0.0528 | 50 | Oral hypoesthesia | 0.0078 |
| 25 | Chest pain | 0.0517 | 51 | Hematuria | 0.0078 |
| 26 | Hypesthesia | 0.0517 | | | |

(*) Subcutaneous hemorrhaging+gingival bleeding+epistaxis.

Sixty-two of the 132 combinations were not marked with "★" or "★★" and were subjected to the calculation.

***CalQ0* and *CalQ+*** The results of the survey and the calculations for the 62 combinations are shown in Table 3.

A simplified list of the *LR+Q0* and *LR+Q+* calculation results, as well as drug names and fully spelt out descriptions of the ADR/AE and IS are shown in Table 4.

For Ti-Ld-Py, which was ranked in first place, $P_{post}Q+$ was not calculated because $Q_{pre}+Q_{non}$ exceeded 1.

The combinations are listed in decreasing order of *LR+Q0* in Tables 3 and 4. Their ranks were similar to those based on *LR+Q+* (rank correlation coefficient: 0.993, calculated excluding Ti-Ld-Py). Thirty combinations had *LR+Q0* values of less than 1; *i.e.*, their $P_{post}$ values were smaller than their $P_{pre}$ values. This was due to the fact that their $Q_{pre}$ values were lower than their associated $Q_{non}$ values, indicating that the incidence of IS-like changes in physical condition that occur during daily life and are unrelated to the medication was higher than the incidence of drug-induced IS; therefore, it would be inappropriate to regard the target symptoms as IS of ADR. Although the *LR+Q+* values of some combinations exceeded 1, most of these combinations exhibited insignificant differences between their $P_{pre}$ and $P_{post}Q+$ values, and the associated symptoms were demonstrated to be inappropriate for detecting the target ADR, as was found in the *LR+Q0*-based evaluation.

**Usefulness of IS** Development of the IS marked with "★" in Table 2 was not described in ADR cases of the drugs, suggesting low-usefulness as predictors. Provision of the information of these IS are not only less beneficial but also may induce only a nocebo effect, to which attention should be paid.[6)]

The combinations for which $P_{post}$ was calculable (Table 3) are summarized according to IS in Table 5. Combinations for which both $P_{post}Q0$ and $P_{post}Q+$ were significantly greater than $P_{pre}$ and *LR+Q0* was greater than 1 were regarded as useful.

As a result, pyrexia was found to be useful in 7 of 10 drug-ADR-IS combinations for which the parameters could be calculated, suggesting its usefulness as an IS. Vomiting (4/5) and decreased appetite (3/6) were also suggested to be useful ADR predictors. Pruritus (0/11) and rash (0/9) are widely informed as IS, but were not found to be useful in any of the drug-ADR-IS combinations examined in this study. However, although pyrexia was considered to be useful, it did not develop in 5 of 15 candidate drug-ADR-IS combinations, which were marked with "★," demonstrating that the type of IS induced and the likelihood of IS developing differ depending on the type of drug and ADR.

To prevent thiamazole-induced agranulocytosis, which was ranked highly in Tables 3 and 4, we suggest that fever should be selected as the IS, whereas paroxetine-induced serotonin syndrome can be detected by selecting tremors, levofloxacin- or terbinafine-induced liver disorder can be predicted by selecting fever, and decreased appetite might be a useful indicator of terbinafine-induced liver dysfunction. All of these IS were selected because they exhibited *LR+* values of greater than 5.0. However, the calculations for fever for ticlopidine-induced liver disorder and decreased appetite for acarbose-induced liver dysfunction may have been less reliable because

Table 2. Selected Drug-ADR-IS Combinations and Results of an AERS Database Search

| ID | Drg | AR | IS | Drug-ADR-IS, abbreviation |
|---|---|---|---|---|
| 1 | Acarbose | Abnormal hepatic function | Decreased appetite | Ac-Hf-Da |
| 2 | Acarbose | Abnormal hepatic function | Malaise★ | Ac-Hf-Ml |
| 3 | Acarbose | Abnormal hepatic function | Nausea★ | Ac-Hf-Na |
| 4 | Acarbose | Abnormal hepatic function | Pruritus★ | Ac-Hf-Pr |
| 5 | Acarbose | Abnormal hepatic function | Pyrexia★ | Ac-Hf-Py |
| 6 | Acarbose | Abnormal hepatic function | Rash★ | Ac-Hf-Ra |
| 7 | Acarbose | Abnormal hepatic function | Vomiting★ | Ac-Hf-Vo |
| 8 | Acarbose | Liver disorder | Decreased appetite★ | Ac-Ld-Da |
| 9 | Acarbose | Liver disorder | Malaise★ | Ac-Ld-Ml |
| 10 | Acarbose | Liver disorder | Nausea★ | Ac-Ld-Na |
| 11 | Acarbose | Liver disorder | Pruritus★ | Ac-Ld-Pr |
| 12 | Acarbose | Liver disorder | Pyrexia★ | Ac-Ld-Py |
| 13 | Acarbose | Liver disorder | Rash★ | Ac-Ld-Ra |
| 14 | Acarbose | Liver disorder | Vomiting★ | Ac-Ld-Vo |
| 15 | Atorvastatin calcium hydrate | Abnormal hepatic function | Decreased appetite | At-Hf-Da |
| 16 | Atorvastatin calcium hydrate | Abnormal hepatic function | Malaise | At-Hf-Ml |
| 17 | Atorvastatin calcium hydrate | Abnormal hepatic function | Nausea | At-Hf-Na |
| 18 | Atorvastatin calcium hydrate | Abnormal hepatic function | Pruritus | At-Hf-Pr |
| 19 | Atorvastatin calcium hydrate | Abnormal hepatic function | Pyrexia | At-Hf-Py |
| 20 | Atorvastatin calcium hydrate | Abnormal hepatic function | Rash | At-Hf-Ra |
| 21 | Atorvastatin calcium hydrate | Abnormal hepatic function | Vomiting | At-Hf-Vo |
| 22 | Atorvastatin calcium hydrate | Liver disorder | Decreased appetite | At-Ld-Da |
| 23 | Atorvastatin calcium hydrate | Liver disorder | Malaise | At-Ld-Ml |
| 24 | Atorvastatin calcium hydrate | Liver disorder | Nausea | At-Ld-Na |
| 25 | Atorvastatin calcium hydrate | Liver disorder | Pruritus★ | At-Ld-Pr |
| 26 | Atorvastatin calcium hydrate | Liver disorder | Pyrexia | At-Ld-Py |
| 27 | Atorvastatin calcium hydrate | Liver disorder | Rash★ | At-Ld-Ra |
| 28 | Atorvastatin calcium hydrate | Liver disorder | Vomiting | At-Ld-Vo |
| 29 | Bezafibrate | Rhabdomyolysis★★ | Asthenia | Be-Rh-As |
| 30 | Bezafibrate | Rhabdomyolysis★★ | Hematuria | Be-Rh-Hu |
| 31 | Bezafibrate | Rhabdomyolysis★★ | Malaise | Be-Rh-Ml |
| 32 | Bezafibrate | Rhabdomyolysis★★ | Myalgia | Be-Rh-My |
| 33 | Cibenzoline succinate | Hypoglycemia★★ | Asthenia | Ci-Hy-As |
| 34 | Cibenzoline succinate | Hypoglycemia★★ | Dizziness | Ci-Hy-Dz |
| 35 | Cibenzoline succinate | Hypoglycemia★★ | Dyslalia | Ci-Hy-Dl |
| 36 | Cibenzoline succinate | Hypoglycemia★★ | Headache | Ci-Hy-Hd |
| 37 | Cibenzoline succinate | Hypoglycemia★★ | Nausea | Ci-Hy-Na |
| 38 | Cibenzoline succinate | Hypoglycemia★★ | Palpitations | Ci-Hy-Pa |
| 39 | Cibenzoline succinate | Hypoglycemia★★ | Somnolence | Ci-Hy-So |
| 40 | Cibenzoline succinate | Hypoglycemia★★ | Tremors | Ci-Hy-Tr |
| 41 | Famotidine | Neutropenia | Oropharyngeal pain★ | Fa-Np-Or |
| 42 | Famotidine | Neutropenia | Pyrexia★ | Fa-Np-Py |
| 43 | Glimepiride | Hypoglycemia | Asthenia | Gl-Hy-As |
| 44 | Glimepiride | Hypoglycemia | Dizziness | Gl-Hy-Dz |
| 45 | Glimepiride | Hypoglycemia | Dyslalia★ | Gl-Hy-Dl |
| 46 | Glimepiride | Hypoglycemia | Headache★ | Gl-Hy-Hd |
| 47 | Glimepiride | Hypoglycemia | Nausea★ | Gl-Hy-Na |
| 48 | Glimepiride | Hypoglycemia | Palpitations★ | Gl-Hy-Pa |
| 49 | Glimepiride | Hypoglycemia | Somnolence★ | Gl-Hy-So |
| 50 | Glimepiride | Hypoglycemia | Tremors | Gl-Hy-Tr |
| 51 | Levofloxacin hydrate | Anaphylactoid reaction | Dyspnoea | Le-Ar-Dn |
| 52 | Levofloxacin hydrate | Anaphylactoid reaction | Palpitations★ | Le-Ar-Pa |
| 53 | Levofloxacin hydrate | Anaphylactoid reaction | Pruritus★ | Le-Ar-Pr |
| 54 | Levofloxacin hydrate | Anaphylactoid reaction | Urticaria | Le-Ar-Ur |
| 55 | Levofloxacin hydrate | Anaphylactoid shock | Dyspnoea | Le-As-Dn |
| 56 | Levofloxacin hydrate | Anaphylactoid shock | Palpitations★ | Le-As-Pa |
| 57 | Levofloxacin hydrate | Anaphylactoid shock | Pruritus★ | Le-As-Pr |
| 58 | Levofloxacin hydrate | Anaphylactoid shock | Urticaria | Le-As-Ur |
| 59 | Levofloxacin hydrate | Abnormal hepatic function | Decreased appetite | Le-Hf-Da |
| 60 | Levofloxacin hydrate | Abnormal hepatic function | Malaise | Le-Hf-Ml |
| 61 | Levofloxacin hydrate | Abnormal hepatic function | Nausea★ | Le-Hf-Na |
| 62 | Levofloxacin hydrate | Abnormal hepatic function | Pruritus★ | Le-Hf-Pr |
| 63 | Levofloxacin hydrate | Abnormal hepatic function | Pyrexia | Le-Hf-Py |
| 64 | Levofloxacin hydrate | Abnormal hepatic function | Rash | Le-Hf-Ra |
| 65 | Levofloxacin hydrate | Abnormal hepatic function | Vomiting★ | Le-Hf-Vo |
| 66 | Levofloxacin hydrate | Liver disorder | Decreased appetite★ | Le-Ld-Da |
| 67 | Levofloxacin hydrate | Liver disorder | Malaise | Le-Ld-Ml |

Table 2. Continued

| ID | Drg | AR | IS | Drug-ADR-IS, abbreviation |
|---|---|---|---|---|
| 68 | Levofloxacin hydrate | Liver disorder | Nausea | Le-Ld-Na |
| 69 | Levofloxacin hydrate | Liver disorder | Pruritus★ | Le-Ld-Pr |
| 70 | Levofloxacin hydrate | Liver disorder | Pyrexia | Le-Ld-Py |
| 71 | Levofloxacin hydrate | Liver disorder | Rash★ | Le-Ld-Ra |
| 72 | Levofloxacin hydrate | Liver disorder | Vomiting | Le-Ld-Vo |
| 73 | Paroxetine hydrochloride hydrate | Serotonin syndrome | Diarrhea | Pa-Ss-Dr |
| 74 | Paroxetine hydrochloride hydrate | Serotonin syndrome | Hyperhidrosis | Pa-Ss-Hh |
| 75 | Paroxetine hydrochloride hydrate | Serotonin syndrome | Pyrexia | Pa-Ss-Py |
| 76 | Paroxetine hydrochloride hydrate | Serotonin syndrome | Tachycardia | Pa-Ss-Ta |
| 77 | Paroxetine hydrochloride hydrate | Serotonin syndrome | Tremors | Pa-Ss-Tr |
| 78 | Pioglitazone hydrochloride | Congestive heart failure | Dyspnoea | Pi-Cf-Dn |
| 79 | Pioglitazone hydrochloride | Congestive heart failure | Fatigue | Pi-Cf-Fg |
| 80 | Pioglitazone hydrochloride | Congestive heart failure | Edema | Pi-Cf-Oe |
| 81 | Raloxifene hydrochloride | Deep vein thrombosis | Chest pain | Ra-Dt-Cp |
| 82 | Raloxifene hydrochloride | Deep vein thrombosis | Dyslalia★ | Ra-Dt-Dl |
| 83 | Raloxifene hydrochloride | Deep vein thrombosis | Dyspnoea | Ra-Dt-Dn |
| 84 | Raloxifene hydrochloride | Venous thrombosis | Chest pain★ | Ra-Vt-Cp |
| 85 | Raloxifene hydrochloride | Venous thrombosis | Dyslalia★ | Ra-Vt-Dl |
| 86 | Raloxifene hydrochloride | Venous thrombosis | Dyspnoea★ | Ra-Vt-Dn |
| 87 | Risperidone | Neuroleptic malignant syndrome | Increased blood pressure | Ri-Nm-Bi |
| 88 | Risperidone | Neuroleptic malignant syndrome | Dyslalia | Ri-Nm-Dl |
| 89 | Risperidone | Neuroleptic malignant syndrome | Hyperhidrosis | Ri-Nm-Hh |
| 90 | Risperidone | Neuroleptic malignant syndrome | Musculoskeletal stiffness | Ri-Nm-Ms |
| 91 | Risperidone | Neuroleptic malignant syndrome | Pyrexia | Ri-Nm-Py |
| 92 | Risperidone | Neuroleptic malignant syndrome | Tachycardia | Ri-Nm-Ta |
| 93 | Risperidone | Neuroleptic malignant syndrome | Tremors | Ri-Nm-Tr |
| 94 | Terbinafine hydrochloride | Abnormal hepatic function | Decreased appetite | Te-Hf-Da |
| 95 | Terbinafine hydrochloride | Abnormal hepatic function | Malaise | Te-Hf-Ml |
| 96 | Terbinafine hydrochloride | Abnormal hepatic function | Nausea | Te-Hf-Na |
| 97 | Terbinafine hydrochloride | Abnormal hepatic function | Pruritus | Te-Hf-Pr |
| 98 | Terbinafine hydrochloride | Abnormal hepatic function | Pyrexia | Te-Hf-Py |
| 99 | Terbinafine hydrochloride | Abnormal hepatic function | Rash★ | Te-Hf-Ra |
| 100 | Terbinafine hydrochloride | Abnormal hepatic function | Vomiting | Te-Hf-Vo |
| 101 | Terbinafine hydrochloride | Liver disorder | Decreased appetite | Te-Ld-Da |
| 102 | Terbinafine hydrochloride | Liver disorder | Malaise | Te-Ld-Ml |
| 103 | Terbinafine hydrochloride | Liver disorder | Nausea | Te-Ld-Na |
| 104 | Terbinafine hydrochloride | Liver disorder | Pruritus | Te-Ld-Pr |
| 105 | Terbinafine hydrochloride | Liver disorder | Pyrexia | Te-Ld-Py |
| 106 | Terbinafine hydrochloride | Liver disorder | Rash | Te-Ld-Ra |
| 107 | Terbinafine hydrochloride | Liver disorder | Vomiting | Te-Ld-Vo |
| 108 | Thiamazole | Agranulocytosis | Oropharyngeal pain | Th-Ag-Or |
| 109 | Thiamazole | Agranulocytosis | Pyrexia | Th-Ag-Py |
| 110 | Ticlopidine hydrochloride | Anemia | Fatigue★ | Ti-An-Fg |
| 111 | Ticlopidine hydrochloride | Anemia | Headache | Ti-An-Hd |
| 112 | Ticlopidine hydrochloride | Anemia | Malaise★ | Ti-An-Ml |
| 113 | Ticlopidine hydrochloride | Anemia | Palpitations★ | Ti-An-Pa |
| 114 | Ticlopidine hydrochloride | Cerebral hemorrhage | Hemorrhage(*)★ | Ti-Ch-Hr |
| 115 | Ticlopidine hydrochloride | Granulocytopenia | Oropharyngeal pain★ | Ti-Gp-Or |
| 116 | Ticlopidine hydrochloride | Granulocytopenia | Pyrexia★ | Ti-Gp-Py |
| 117 | Ticlopidine hydrochloride | Liver disorder | Decreased appetite★ | Ti-Ld-Da |
| 118 | Ticlopidine hydrochloride | Liver disorder | Malaise★ | Ti-Ld-Ml |
| 119 | Ticlopidine hydrochloride | Liver disorder | Nausea★ | Ti-Ld-Na |
| 120 | Ticlopidine hydrochloride | Liver disorder | Pruritus★ | Ti-Ld-Pr |
| 121 | Ticlopidine hydrochloride | Liver disorder | Pyrexia | Ti-Ld-Py |
| 122 | Ticlopidine hydrochloride | Liver disorder | Rash★ | Ti-Ld-Ra |
| 123 | Ticlopidine hydrochloride | Liver disorder | Vomiting★ | Ti-Ld-Vo |
| 124 | Ticlopidine hydrochloride | Pancytopenia | Dizziness★ | Ti-Pp-Dz |
| 125 | Ticlopidine hydrochloride | Pancytopenia | Dyspnoea★ | Ti-Pp-Dn |
| 126 | Ticlopidine hydrochloride | Pancytopenia | Fatigue★ | Ti-Pp-Fg |
| 127 | Ticlopidine hydrochloride | Pancytopenia | Hematuria★ | Ti-Pp-Hu |
| 128 | Ticlopidine hydrochloride | Pancytopenia | Hemorrhage(*)★ | Ti-Pp-Hr |
| 129 | Ticlopidine hydrochloride | Pancytopenia | Oropharyngeal pain★ | Ti-Pp-Or |
| 130 | Ticlopidine hydrochloride | Pancytopenia | Palpitations★ | Ti-Pp-Pa |
| 131 | Ticlopidine hydrochloride | Pancytopenia | Pyrexia★ | Ti-Pp-Py |
| 132 | Ticlopidine hydrochloride | Thrombocytopenia | Hemorrhage(*)★ | Ti-Tp-Hr |

(*) Subcutaneous hemorrhaging+gingival bleeding+epistaxis. ★ This IS was not reported. ★★ This ADR was not reported in cases involving monotherapy.

Table 3. Calculations and Survey Results for 62 Drug-ADR-IS Combinations

| Rank | ID | Drug-ADR-IS abbreviation | PMS | | | AERS (single drug therapy) | | | | $Q_{pre}$ | $Q_{non}$ | $P_{pre}$ | *CalQ0* | | | *CalQ+* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Surveyed cases ① | Total ADR cases ② | Target ADR cases ③ | Total ADR/AE cases ④ | Target ADR/AE cases ⑤ | Total ADR/AE cases with IS ⑥ | Target ADR/AE cases with IS ⑦ | | | | $P_{post}Q0$ | Sig. level *vs.* $P_{pre}$ (※1) | $LR+Q0$ | $P_{post}Q+$ | Sig. level *vs.* $P_{pre}$ (※1) | $LR+Q+$ |
| 1 | 121 | Ti-Ld-Py | 6813 | 461 | 1 | 1609 | 1 | 44 | 1 | 1.0000000 | 0.0350000 | 0.0001468 | 0.0042441 | **** | 29.03 | — | — | — |
| 2 | 109 | Th-Ag-Py | 732 | 82 | 5 | 1318 | 23 | 37 | 11 | 0.4782609 | 0.0350000 | 0.0068306 | 0.0896047 | **** | 14.31 | 0.0868249 | **** | 13.82 |
| 3 | 1 | Ac-Hf-Da | 3634 | 799 | 2 | 379 | 3 | 3 | 1 | 0.3333333 | 0.0377778 | 0.0005504 | 0.0059521 | **** | 10.87 | 0.0052199 | *** | 9.53 |
| 4 | 77 | Pa-Ss-Tr | 5561 | 1201 | 2 | 76523 | 103 | 1098 | 18 | 0.1747573 | 0.0194444 | 0.0003596 | 0.0034242 | *** | 9.55 | 0.0030967 | *** | 8.63 |
| 5 | 70 | Le-Ld-Py | 29880 | 482 | 8 | 28536 | 13 | 129 | 3 | 0.2307692 | 0.0350000 | 0.0002677 | 0.0017874 | **** | 6.69 | 0.0020254 | **** | 7.58 |
| 6 | 105 | Te-Ld-Py | 6929 | 825 | 23 | 11153 | 56 | 130 | 11 | 0.1964286 | 0.0350000 | 0.0033194 | 0.0199237 | **** | 6.10 | 0.0208222 | **** | 6.39 |
| 7 | 94 | Te-Hf-Da | 6929 | 825 | 62 | 11153 | 46 | 102 | 8 | 0.1739130 | 0.0377778 | 0.0089479 | 0.0435071 | **** | 5.04 | 0.0470420 | **** | 5.47 |
| 8 | 78 | Pi-Cf-Dn | 3421 | 556 | 1 | 4263 | 135 | 98 | 16 | 0.1185185 | 0.0250000 | 0.0002923 | 0.0014319 | NS | 4.90 | 0.0014847 | NS | 5.09 |
| 9 | 98 | Te-Hf-Py | 6929 | 825 | 62 | 11153 | 46 | 130 | 7 | 0.1521739 | 0.0350000 | 0.0089479 | 0.0407507 | **** | 4.71 | 0.0445653 | **** | 5.17 |
| 10 | 76 | Pa-Ss-Ta | 5561 | 1201 | 2 | 76523 | 103 | 60 | 10 | 0.0970874 | 0.0288889 | 0.0003596 | 0.0015297 | * | 4.26 | 0.0015588 | * | 4.34 |
| 11 | 72 | Le-Ld-Vo | 29880 | 482 | 8 | 28536 | 13 | 138 | 1 | 0.0769231 | 0.0188889 | 0.0002677 | 0.0011025 | **** | 4.12 | 0.0013511 | **** | 5.05 |
| 12 | 75 | Pa-Ss-Py | 5561 | 1201 | 2 | 76523 | 103 | 167 | 10 | 0.0970874 | 0.0350000 | 0.0003596 | 0.0012507 | NS | 3.48 | 0.0013390 | NS | 3.73 |
| 13 | 91 | Ri-Nm-Py | 3902 | 1025 | 7 | 17201 | 122 | 78 | 11 | 0.0901639 | 0.0350000 | 0.0017940 | 0.0059927 | ** | 3.35 | 0.0062052 | ** | 3.47 |
| 14 | 103 | Te-Ld-Na | 6929 | 825 | 23 | 11153 | 56 | 152 | 7 | 0.1250000 | 0.0427778 | 0.0033194 | 0.0104747 | **** | 3.18 | 0.0124576 | **** | 3.79 |
| 15 | 107 | Te-Ld-Vo | 6929 | 825 | 23 | 11153 | 56 | 65 | 3 | 0.0535714 | 0.0188889 | 0.0033194 | 0.0101821 | **** | 3.09 | 0.0122010 | **** | 3.71 |
| 16 | 74 | Pa-Ss-Hh | 5561 | 1201 | 2 | 76523 | 103 | 1025 | 11 | 0.1067961 | 0.0405556 | 0.0003596 | 0.0011070 | NS | 3.08 | 0.0012195 | NS | 3.39 |
| 17 | 21 | At-Hf-Vo | 4805 | 576 | 68 | 32932 | 38 | 80 | 2 | 0.0526316 | 0.0188889 | 0.0141519 | 0.0422720 | **** | 3.07 | 0.0509018 | **** | 3.74 |
| 18 | 63 | Le-Hf-Py | 29880 | 482 | 14 | 28536 | 20 | 129 | 2 | 0.1000000 | 0.0350000 | 0.0004685 | 0.0013560 | *** | 2.90 | 0.0018012 | **** | 3.85 |
| 19 | 80 | Pi-Cf-Oe | 3421 | 556 | 1 | 4263 | 135 | 106 | 15 | 0.1111111 | 0.0438889 | 0.0002923 | 0.0008046 | NS | 2.75 | 0.0009539 | NS | 3.27 |
| 20 | 100 | Te-Hf-Vo | 6929 | 825 | 62 | 11153 | 46 | 65 | 2 | 0.0434783 | 0.0188889 | 0.0089479 | 0.0220375 | **** | 2.50 | 0.0280394 | **** | 3.20 |
| 21 | 102 | Te-Ld-Ml | 6929 | 825 | 23 | 11153 | 56 | 97 | 16 | 0.2857143 | 0.1338889 | 0.0033194 | 0.0079204 | *** | 2.40 | 0.0102653 | **** | 3.11 |
| 22 | 101 | Te-Ld-Da | 6929 | 825 | 23 | 11153 | 56 | 102 | 4 | 0.0714286 | 0.0377778 | 0.0033194 | 0.0068647 | ** | 2.08 | 0.0092860 | **** | 2.81 |
| 23 | 108 | Th-Ag-Or | 732 | 82 | 5 | 1318 | 23 | 16 | 3 | 0.1304348 | 0.0783333 | 0.0068306 | 0.0124599 | NS | 1.83 | 0.0177629 | NS | 2.63 |
| 24 | 68 | Le-Ld-Na | 29880 | 482 | 8 | 28536 | 13 | 289 | 1 | 0.0769231 | 0.0427778 | 0.0002677 | 0.0004872 | NS | 1.82 | 0.0007460 | * | 2.79 |
| 25 | 96 | Te-Hf-Na | 6929 | 825 | 62 | 11153 | 46 | 152 | 3 | 0.0652174 | 0.0427778 | 0.0089479 | 0.0146825 | ** | 1.65 | 0.0215513 | **** | 2.44 |
| 26 | 93 | Ri-Nm-Tr | 3902 | 1025 | 7 | 17201 | 122 | 121 | 3 | 0.0245902 | 0.0194444 | 0.0017940 | 0.0027259 | NS | 1.52 | 0.0037103 | NS | 2.07 |
| 27 | 95 | Te-Hf-Ml | 6929 | 825 | 62 | 11153 | 46 | 97 | 8 | 0.1739130 | 0.1338889 | 0.0089479 | 0.0129264 | * | 1.45 | 0.0202027 | **** | 2.28 |
| 28 | 51 | Le-Ar-Dn | 29880 | 482 | 1 | 28536 | 57 | 313 | 2 | 0.0350877 | 0.0250000 | 0.0000335 | 0.0000474 | NS | 1.42 | 0.0000799 | NS | 2.39 |
| 29 | 24 | At-Ld-Na | 4805 | 576 | 11 | 32932 | 131 | 202 | 7 | 0.0534351 | 0.0427778 | 0.0022893 | 0.0031797 | NS | 1.39 | 0.0050519 | * | 2.21 |
| 30 | 59 | Le-Hf-Da | 29880 | 482 | 14 | 28536 | 20 | 99 | 1 | 0.0500000 | 0.0377778 | 0.0004685 | 0.0006290 | NS | 1.34 | 0.0010864 | ** | 2.32 |
| 31 | 89 | Ri-Nm-Hh | 3902 | 1025 | 7 | 17201 | 122 | 47 | 5 | 0.0409836 | 0.0405556 | 0.0017940 | 0.0024013 | NS | 1.34 | 0.0035443 | NS | 1.98 |
| 32 | 92 | Ri-Nm-Ta | 3902 | 1025 | 7 | 17201 | 122 | 105 | 3 | 0.0245902 | 0.0288889 | 0.0017940 | 0.0019262 | NS | 1.07 | 0.0031465 | NS | 1.76 |
| 33 | 83 | Ra-Dt-Dn | 6967 | 776 | 7 | 6770 | 137 | 51 | 3 | 0.0218978 | 0.0250000 | 0.0010047 | 0.0009551 | NS | 0.95 | 0.0018249 | NS | 1.82 |
| 34 | 73 | Pa-Ss-Dr | 5561 | 1201 | 2 | 76523 | 103 | 634 | 8 | 0.0776699 | 0.1161111 | 0.0003596 | 0.0003009 | NS | 0.84 | 0.0005911 | NS | 1.64 |
| 35 | 19 | At-Hf-Py | 4805 | 576 | 68 | 32932 | 38 | 97 | 1 | 0.0263158 | 0.0350000 | 0.0141519 | 0.0118283 | NS | 0.83 | 0.0243193 | *** | 1.74 |
| 36 | 15 | At-Hf-Da | 4805 | 576 | 68 | 32932 | 38 | 50 | 1 | 0.0263158 | 0.0377778 | 0.0141519 | 0.0110251 | NS | 0.78 | 0.0236779 | *** | 1.69 |
| 37 | 50 | Gl-Hy-Tr | 3409 | 146 | 49 | 1095 | 68 | 5 | 1 | 0.0147059 | 0.0194444 | 0.0143737 | 0.0111640 | NS | 0.77 | 0.0248331 | ** | 1.75 |
| 38 | 43 | Gl-Hy-As | 3409 | 146 | 49 | 1095 | 68 | 11 | 1 | 0.0147059 | 0.0200000 | 0.0143737 | 0.0107671 | NS | 0.75 | 0.0243480 | ** | 1.71 |
| 39 | 55 | Le-As-Dn | 29880 | 482 | 1 | 28536 | 55 | 313 | 1 | 0.0181818 | 0.0250000 | 0.0000335 | 0.0000246 | NS | 0.73 | 0.0000574 | NS | 1.72 |
| 40 | 106 | Te-Ld-Ra | 6929 | 825 | 23 | 11153 | 56 | 144 | 3 | 0.0535714 | 0.0833333 | 0.0033194 | 0.0023691 | NS | 0.71 | 0.0053475 | * | 1.61 |

Table 3. Continued

| Rank | ID | Drug-ADR-IS abbreviation | PMS | | | AERS (single drug therapy) | | | | $Q_{pre}$ | $Q_{non}$ | $P_{pre}$ | *CalQ0* | | | *CalQ+* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Surveyed cases ① | Total ADR cases ② | Target ADR cases ③ | Total ADR/AE cases ④ | Target ADR/AE cases ⑤ | Total ADR/AE cases with IS ⑥ | Target ADR/AE cases with IS ⑦ | | | | $P_{post}Q0$ | Sig. level *vs.* $P_{pre}$ (※1) | $LR+Q0$ | $P_{post}Q+$ | Sig. level *vs.* $P_{pre}$ (※1) | $LR+Q+$ |
| 41 | 17 | At-Hf-Na | 4805 | 576 | 68 | 32932 | 38 | 202 | 1 | 0.0263158 | 0.0427778 | 0.0141519 | 0.0096311 | * | 0.68 | 0.0223263 | ** | 1.59 |
| 42 | 111 | Ti-An-Hd | 6813 | 461 | 13 | 1609 | 14 | 11 | 1 | 0.0714286 | 0.1250000 | 0.0019081 | 0.0011640 | NS | 0.61 | 0.0029854 | NS | 1.57 |
| 43 | 64 | Le-Hf-Ra | 29880 | 482 | 14 | 28536 | 20 | 214 | 1 | 0.0500000 | 0.0833333 | 0.0004685 | 0.0002852 | NS | 0.61 | 0.0007484 | NS | 1.60 |
| 44 | 67 | Le-Ld-Ml | 29880 | 482 | 8 | 28536 | 13 | 132 | 1 | 0.0769231 | 0.1338889 | 0.0002677 | 0.0001562 | NS | 0.58 | 0.0004213 | NS | 1.57 |
| 45 | 54 | Le-Ar-Ur | 29880 | 482 | 1 | 28536 | 57 | 176 | 2 | 0.0350877 | 0.0614192 | 0.0000335 | 0.0000194 | NS | 0.58 | 0.0000525 | NS | 1.57 |
| 46 | 88 | Ri-Nm-Dl | 3902 | 1025 | 7 | 17201 | 122 | 1 | 1 | 0.0081967 | 0.0205556 | 0.0017940 | 0.0009693 | NS | 0.54 | 0.0025075 | NS | 1.40 |
| 47 | 97 | Te-Hf-Pr | 6929 | 825 | 62 | 11153 | 46 | 204 | 3 | 0.0652174 | 0.1450000 | 0.0089479 | 0.0044782 | ** | 0.50 | 0.0127460 | * | 1.43 |
| 48 | 26 | At-Ld-Py | 4805 | 576 | 11 | 32932 | 131 | 97 | 2 | 0.0152672 | 0.0350000 | 0.0022893 | 0.0011209 | NS | 0.49 | 0.0032530 | NS | 1.42 |
| 49 | 28 | At-Ld-Vo | 4805 | 576 | 11 | 32932 | 131 | 80 | 1 | 0.0076336 | 0.0188889 | 0.0022893 | 0.0010325 | NS | 0.45 | 0.0031641 | NS | 1.38 |
| 50 | 23 | At-Ld-Ml | 4805 | 576 | 11 | 32932 | 131 | 195 | 7 | 0.0534351 | 0.1338889 | 0.0022893 | 0.0010311 | NS | 0.45 | 0.0031840 | NS | 1.39 |
| 51 | 87 | Ri-Nm-Bi | 3902 | 1025 | 7 | 17201 | 122 | 16 | 2 | 0.0163934 | 0.0494444 | 0.0017940 | 0.0008014 | NS | 0.45 | 0.0023770 | NS | 1.33 |
| 52 | 16 | At-Hf-Ml | 4805 | 576 | 68 | 32932 | 38 | 195 | 2 | 0.0526316 | 0.1338889 | 0.0141519 | 0.0062484 | *** | 0.44 | 0.0195160 | * | 1.39 |
| 53 | 18 | At-Hf-Pr | 4805 | 576 | 68 | 32932 | 38 | 104 | 2 | 0.0526316 | 0.1450000 | 0.0141519 | 0.0057878 | **** | 0.41 | 0.0191471 | NS | 1.36 |
| 54 | 90 | Ri-Nm-Ms | 3902 | 1025 | 7 | 17201 | 122 | 45 | 2 | 0.0163934 | 0.0572222 | 0.0017940 | 0.0006859 | NS | 0.38 | 0.0022805 | NS | 1.27 |
| 55 | 60 | Le-Hf-Ml | 29880 | 482 | 14 | 28536 | 20 | 132 | 1 | 0.0500000 | 0.1338889 | 0.0004685 | 0.0001777 | * | 0.38 | 0.0006431 | NS | 1.37 |
| 56 | 20 | At-Hf-Ra | 4805 | 576 | 68 | 32932 | 38 | 125 | 1 | 0.0263158 | 0.0833333 | 0.0141519 | 0.0050249 | **** | 0.35 | 0.0184503 | NS | 1.31 |
| 57 | 44 | Gl-Hy-Dz | 3409 | 146 | 49 | 1095 | 68 | 8 | 2 | 0.0294118 | 0.0861111 | 0.0143737 | 0.0050927 | **** | 0.35 | 0.0191521 | NS | 1.34 |
| 58 | 81 | Ra-Dt-Cp | 6967 | 776 | 7 | 6770 | 137 | 47 | 2 | 0.0145985 | 0.0516667 | 0.0010047 | 0.0003142 | NS | 0.31 | 0.0012699 | NS | 1.26 |
| 59 | 58 | Le-As-Ur | 29880 | 482 | 1 | 28536 | 55 | 176 | 1 | 0.0181818 | 0.0614192 | 0.0000335 | 0.0000101 | NS | 0.30 | 0.0000433 | NS | 1.29 |
| 60 | 104 | Te-Ld-Pr | 6929 | 825 | 23 | 11153 | 56 | 204 | 2 | 0.0357143 | 0.1450000 | 0.0033194 | 0.0009122 | ** | 0.27 | 0.0040744 | NS | 1.23 |
| 61 | 22 | At-Ld-Da | 4805 | 576 | 11 | 32932 | 131 | 50 | 1 | 0.0076336 | 0.0377778 | 0.0022893 | 0.0005226 | * | 0.23 | 0.0027379 | NS | 1.20 |
| 62 | 79 | Pi-Cf-Fg | 3421 | 556 | 1 | 4263 | 135 | 55 | 2 | 0.0148148 | 0.1644444 | 0.0002923 | 0.0000310 | NS | 0.11 | 0.0003147 | NS | 1.08 |

※1 ****$p<0.0001$, ***$0.0001<p<0.001$, **$0.001<p<0.01$, *$0.01<p<0.05$. $P_{pre}$ =③/① $P_{other}$=(②−③)/① $P_{non}$=1−$P_{pre}$−$P_{other}$ $Q_{pre}$=⑦/⑤ $Q_{other}$=(⑥−⑦)/(④−⑤)

Table 4. Summary of Table 3

| Rank | ID | Drug | ADR/AE | IS | *LR+Q0* | *LR+Q+* | Rank | ID | Drug | ADR/AE | IS | *LR+Q0* | *LR+Q+* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 121 | Ticlopidine | Liver disorder | Pyrexia | **29.03** | — | 32 | 92 | Risperidone | Neuroleptic malignant syndrome | Tachycardia | *1.07* | *1.76* |
| 2 | 109 | Thiamazole | Agranulocytosis | Pyrexia | **14.31** | **13.82** | 33 | 83 | Raloxifene | Deep vein thrombosis | Dyspnoea | *0.95* | *1.82* |
| 3 | 1 | Acarbose | Abnormal hepatic function | Decreased appetite | **10.87** | **9.53** | 34 | 73 | Paroxetine | Serotonin syndrome | Diarrhea | *0.84* | *1.64* |
| 4 | 77 | Paroxetine | Serotonin syndrome | Tremors | **9.55** | **8.63** | 35 | 19 | Atorvastatin | Abnormal hepatic function | Pyrexia | *0.83* | **1.74** |
| 5 | 70 | Levofloxacin | Liver disorder | Pyrexia | **6.69** | **7.58** | 36 | 15 | Atorvastatin | Abnormal hepatic function | Decreased appetite | *0.78* | **1.69** |
| 6 | 105 | Terbinafine | Liver disorder | Pyrexia | **6.10** | **6.39** | 37 | 50 | Glimepiride | Hypoglycemia | Tremors | *0.77* | **1.75** |
| 7 | 94 | Terbinafine | Abnormal hepatic function | Decreased appetite | **5.04** | **5.47** | 38 | 43 | Glimepiride | Hypoglycemia | Asthenia | *0.75* | **1.71** |
| 8 | 78 | Pioglitazone | Congestive heart failure | Dyspnoea | *4.90* | *5.09* | 39 | 55 | Levofloxacin | Anaphylactoid shock | Dyspnoea | *0.73* | *1.72* |
| 9 | 98 | Terbinafine | Abnormal hepatic function | Pyrexia | **4.71** | **5.17** | 40 | 106 | Terbinafine | Liver disorder | Rash | *0.71* | **1.61** |
| 10 | 76 | Paroxetine | Serotonin syndrome | Tachycardia | **4.26** | **4.34** | 41 | 17 | Atorvastatin | Abnormal hepatic function | Nausea | **0.68** | **1.59** |
| 11 | 72 | Levofloxacin | Liver disorder | Vomiting | **4.12** | **5.05** | 42 | 111 | Ticlopidine | Anemia | Headache | *0.61* | *1.57* |
| 12 | 75 | Paroxetine | Serotonin syndrome | Pyrexia | *3.48* | *3.73* | 43 | 64 | Levofloxacin | Abnormal hepatic function | Rash | *0.61* | *1.60* |
| 13 | 91 | Risperidone | Neuroleptic malignant s yndrome | Pyrexia | **3.35** | **3.47** | 44 | 67 | Levofloxacin | Liver disorder | Malaise | *0.58* | *1.57* |
| 14 | 103 | Terbinafine | Liver disorder | Nausea | **3.18** | **3.79** | 45 | 54 | Levofloxacin | Anaphylactoid reaction | Urticaria | *0.58* | *1.57* |
| 15 | 107 | Terbinafine | Liver disorder | Vomiting | **3.09** | **3.71** | 46 | 88 | Risperidone | Neuroleptic malignant syndrome | Dyslalia | *0.54* | *1.40* |
| 16 | 74 | Paroxetine | Serotonin syndrome | Hyperhidrosis | *3.08* | *3.39* | 47 | 97 | Terbinafine | Abnormal hepatic function | Pruritus | **0.50** | **1.43** |
| 17 | 21 | Atorvastatin | Abnormal hepatic function | Vomiting | **3.07** | **3.74** | 48 | 26 | Atorvastatin | Liver disorder | Pyrexia | *0.49* | *1.42* |
| 18 | 63 | Levofloxacin | Abnormal hepatic function | Pyrexia | **2.90** | **3.85** | 49 | 28 | Atorvastatin | Liver disorder | Vomiting | *0.45* | *1.38* |
| 19 | 80 | Pioglitazone | Congestive heart failure | Edema | *2.75* | *3.27* | 50 | 23 | Atorvastatin | Liver disorder | Malaise | *0.45* | *1.39* |
| 20 | 100 | Terbinafine | Abnormal hepatic function | Vomiting | **2.50** | **3.20** | 51 | 87 | Risperidone | Neuroleptic malignant syndrome | Increased blood pressure | *0.45* | *1.33* |
| 21 | 102 | Terbinafine | Liver disorder | Malaise | **2.40** | **3.11** | 52 | 16 | Atorvastatin | Abnormal hepatic function | Malaise | **0.44** | **1.39** |
| 22 | 101 | Terbinafine | Liver disorder | Decreased appetite | **2.08** | **2.81** | 53 | 18 | Atorvastatin | Abnormal hepatic function | Pruritus | **0.41** | *1.36* |
| 23 | 108 | Thiamazole | Agranulocytosis | Oropharyngeal pain | *1.83* | *2.63* | 54 | 90 | Risperidone | Neuroleptic malignant syndrome | Musculos keletal stiffness | *0.38* | *1.27* |
| 24 | 68 | Levofloxacin | Liver disorder | Nausea | *1.82* | **2.79** | 55 | 60 | Levofloxacin | Abnormal hepatic function | Malaise | **0.38** | *1.37* |
| 25 | 96 | Terbinafine | Abnormal hepatic function | Nausea | **1.65** | **2.44** | 56 | 20 | Atorvastatin | Abnormal hepatic function | Rash | **0.35** | *1.31* |
| 26 | 93 | Risperidone | Neuroleptic malignant syndrome | Tremors | *1.52* | *2.07* | 57 | 44 | Glimepiride | Hypoglycemia | Dizziness | **0.35** | *1.34* |
| 27 | 95 | Terbinafine | Abnormal hepatic function | Malaise | **1.45** | **2.28** | 58 | 81 | Raloxifene | Deep vein thrombosis | Chest pain | *0.31* | *1.26* |
| 28 | 51 | Levofloxacin | Anaphylactoid reaction | Dyspnoea | *1.42* | *2.39* | 59 | 58 | Levofloxacin | Anaphylactoid shock | Urticaria | *0.30* | *1.29* |
| 29 | 24 | Atorvastatin | Liver disorder | Nausea | *1.39* | **2.21** | 60 | 104 | Terbinafine | Liver disorder | Pruritus | **0.27** | *1.23* |
| 30 | 59 | Levofloxacin | Abnormal hepatic function | Decreased appetite | *1.34* | **2.32** | 61 | 22 | Atorvastatin | Liver disorder | Decreased appetite | **0.23** | *1.20* |
| 31 | 89 | Risperidone | Neuroleptic malignant s yndrome | Hyperhidrosis | *1.34* | *1.98* | 62 | 79 | Pioglitazone | Congestive heart failure | Fatigue | *0.11* | *1.08* |

Likelihood ratios in bold: $p<0.05$ ($P_{pre}$ *vs.* $P_{post}$), Likelihood ratios in italics: Not significant ($P_{pre}$ *vs.* $P_{post}$).

Table 5. Usefulness of IS

| ID | IS | Listed (*X*) | Calculated (*Y*) | Useful (*Z*) |
|---|---|---|---|---|
| 37 | Pyrexia | 15 | 10 | 7 |
| 47 | Vomiting | 9 | 5 | 4 |
| 36 | Decreased appetite | 9 | 6 | 3 |
| 3 | Malaise | 10 | 6 | 2 |
| 30 | Nausea | 10 | 5 | 2 |
| 45 | Tremors | 3 | 3 | 1 |
| 39 | Tachycardia | 2 | 2 | 1 |
| 40 | Dysponea | 6 | 4 | 0 |
| 2 | Pruritus | 11 | 3 | 0 |
| 12 | Rash | 9 | 3 | 0 |
| 33 | Hyperhidrosis | 2 | 2 | 0 |
| 18 | Urticaria | 2 | 2 | 0 |
| 43 | Dyslalia | 4 | 1 | 0 |
| 15 | Oropharyngeal pain | 4 | 1 | 0 |
| 1 | Fatigue | 3 | 1 | 0 |
| 25 | Chest pain | 2 | 1 | 0 |
| 11 | Dizziness | 2 | 1 | 0 |
| 4 | Headache | 2 | 1 | 0 |
| 44 | Asthenia | 1 | 1 | 0 |
| 27 | Increased blood pressure | 1 | 1 | 0 |
| 5 | Diarrhea | 1 | 1 | 0 |
| 32 | Musculoskeletal stiffness | 1 | 1 | 0 |
| 29 | Edema | 1 | 1 | 0 |
| 19 | Palpitations | 5 | 0 | 0 |
| 22 | Hemorrhage(*) | 3 | 0 | 0 |
| 49 | Hematuria | 1 | 0 | 0 |
| 33 | Somnolence | 1 | 0 | 0 |

*X*: number of entries in Table 2, *Y*: number of drug-ADR-IS for which $LR+$ could be calculated, *Z*: number of drug-ADR-IS for which $P_{post}Q0$ and $P_{post}Q+$ were significantly different from $P_{pre}$ and $LR+Q0 > 1$. (*) Subcutaneous hemorrhaging+gingival bleeding+epistaxis.

the numbers of ADR cases and ADR accompanied by IS were small.

## DISCUSSION

**IS That Were Not Reported to the AERS (★)** Some of the ISs listed in the MHD were not reported in the AERS database. In the MHD, the drug-ADR-IS combinations were selected based on their clinical significance. On the other hand, about 40% of the events in the AERS database were reported by customers.[7] In addition, most of them were reported after ADR had developed. Therefore, minor changes might have been overlooked in the AERS database, which might have contributed to some of the drug-ADR-IS combinations not being included in the AERS database.

Thus, the IS included in such drug-ADR-IS combinations might be hard to identify by retrospective studies.

**ADR/AE That Were Not Found in the AERS Database (★★)** No cases of bezafibrate-associated rhabdomyolysis or cibenzoline succinate-associated hypoglycemia were found in the AERS database. It is known that bezafibrate-associated rhabdomyolysis is mainly caused by co-treatment with HMG-CoA reductase inhibitors.[8] In this study, the AERS search was limited to cases involving monotherapy might explain why no cases were identified. In addition, cibenzoline succinate-associated hypoglycemia frequently develops in patients with renal dysfunction.[9] Since most patients with renal dysfunction are prescribed multiple drugs, it is reasonable that no cases were identified when the AERS search was limited to monotherapy-treated patients.

In Japan, package inserts are included with all drugs. These inserts are official documents and provide comprehensive information about the drug in question. Since safety is the primary concern during the production of these package inserts, the reporting of not only ADR that occur in the setting of monotherapy but also those that occur during combination treatment anywhere in the world is requested by the Japanese regulatory authority.[10] Thus the searching for ADR that occurs in monotherapy setting, using official document focusing on safety, might result in some ADR being missed.

***LR+Q0* and *LR+Q+*** $LR+Q+$ was calculated as well as $LR+Q0$ because it was assumed that the individuals with monotherapy that had reported the AE strongly suspected that the drug in question was the cause of the reported AE, and AE that were not caused by the drug were not included in the database. Accordingly, $Q_{non}$ was not included in $Q_{pre}$ or $Q_{other}$. Thus, we added $Q_{non}$ in another calculation to set 2 ranges of $P_{post}$; $P_{post}Q0$ and $P_{post}Q+$, to avoid biased conclusion. This procedure also aimed at avoidance of $LR+$ below 1. That is, the higher the $Q_{non}$ to $Q_{pre}$ ratio, the larger the difference between $LR+Q0$ and $LR+Q+$; *i.e.*, $LR+Q0$ is less than 1 and shifts closer to zero, whereas $LR+Q+$ shifts towards 1.

However, the results of the 2 calculations were mostly the same with regard to the usefulness of the target IS as a predictor of ADR in all calculations, showing that consistent evaluation is possible. Even though a mixture of ADR and AE are included the AERS reports, they might be sufficiently useful to allow the feasibility of IS as predictors of ADR to be evaluated.

**Problems Associated with the Use of Useful IS as Predictive Markers** In this study, we found that pyrexia and vomiting are useful for predicting severe ADR. However, using such IS could be problematic since telling patients about these potential problems might cause them to become anxious, leading to poor adherence. However, providing information about IS that do not make patients as anxious, such as skin symptoms, including rash and pruritus, and fatigue, might be provided frequently rather than useful IS. Thus, in the clinical setting the information provided to patients about IS should be selected carefully.

**Re-calculation of Values Obtained in Our Previous Study[1] Using Eq. 2** Equation 2 was derived from Eq. 1, which was newly developed in the present study. Since $Qt$ is included in Eq. 2, it is only applicable when the total number of users of the target drug is known. In our previous study, we utilized a simplified method to obtain $P_{post}Q+$, and $LR+Q+$ was derived from $P_{post}Q+$.[1] In this study, it was possible to calculate $P_{post}Q+$ and $LR+Q+$ using Eq. 2. When we recalculated the values obtained in our previous study using Eq. 2, we found that the $LR+Q0$ and $LR+Q+$ were similar (Table 6).

**Data Sources and Study Limitations** We used the following variables to perform the calculations in this study: (1) ADR probability values ($P_{pre}$ and $P_{other}$), (2) the incidences of cases in which the target IS was accompanied by ADR/AE ($Q_{pre}$ and $Q_{other}$), and (3) the incidence of I-like symptoms that are not drug-related ($Q_{non}$). The ADR probability values were obtained from the PMS data reported in drug IF, the IS

Table 6. Comparison of $P_{post}Q+$ and $LR+Q+$Values Derived from Eq. 2 with Those Obtained Using a Simplified Method

| | $P_{pre}$ | $P_{post}\ Q+$ | | $LR+Q0$ | $LR+Q+$ | |
|---|---|---|---|---|---|---|
| | | Previous | Eq. 2 | Previous | Previous | Eq. 2 |
| Voriconazole | 0.05000 | 0.04045 | 0.09814 | 5.00 | 0.80 | 2.07 |
| Fenofibrate | 0.00341 | 0.00313 | 0.04512 | 10.82 | 0.92 | 13.79 |
| Sulfametoxazole/trimetoprim | 0.00091 | 0.00329 | 0.01616 | 21.48 | 3.64 | 18.09 |
| Ticlopidine hydrochloride | 0.00176 | 0.00055 | 0.00863 | 2.54 | 0.31 | 4.93 |
| Itraconazole | 0.00081 | 0.00026 | 0.00545 | 4.44 | 0.32 | 6.80 |
| Loxoprofen sodium hydrate | 0.00007 | 0.00017 | 0.00141 | 27.92 | 2.35 | 19.00 |

incidence data were derived from the AERS database, and the data regarding I-like symptoms that are not drug-related were obtained from an internet-based survey of the general public. Each data source has its own problems.

In Japan, PMS data is collected during clinical practice. Although the resultant PMS data might be affected by selection bias because of the limited number of participating centers and the enrollment of agreeable patient,[11] a certain level of quality is assured by the regulatory body since data are collected by pharmaceutical companies under the supervision of the regulatory body.[12] Furthermore, as the total number of patients that take a particular drug can be obtained from the PMS data, the incidence of ADR is calculable.[12] Therefore we used PMS data for calculating $P_{pre}$ and $P_{other}$. However, it was difficult to evaluate the rare ADR, since the sample size was small. Similarly, it was difficult to determine the IS accompanied by ADR from the PMS data. A recent report suggested that small changes in the body condition caused by medication cannot be detected from the PMS data.[13] In the present study, we calculated $Q_{pre}$ and $Q_{other}$ using AERS data. Since the AERS database is based on a spontaneous reporting system, it has a tendency of underreporting to a greater extent than the abovementioned PMS data.[11,14,15] However, the cases in the AERS database involve nearly 5 million subjects, which is a sufficient number to compensate for any such underreporting. On the other hand, since the total number of users of a particular drug cannot be obtained from the AERS database, ADR incidences cannot be derived from it. However, this is not a problem for calculating $Q_{pre}$ and $Q_{other}$ since these parameters represent incidence rates among AE cases associated with the target drug. However, causal relationships have not been demonstrated to exist between the AE reported in the AERS database and the suspected drugs, and some of the reported IS might have been caused by the disease being treated.[14] Our results might have been influenced by these factors. Although notoriety bias (due to increased vigilance following safety alerts) has been detected in the AERS databses,[16] this might not have influenced the IS incidence data examined in our study, because IS is the mild ADR/AE. Finally, $Q_{non}$ was obtained from an internet-based survey. Internet-based research (IR) has attracted attention due to the fact that it allows a large amount of data to be obtained cheaply and quickly. Such data are derived from individuals that are registered with research firms. The quality difference (survey results) between research firms is considered to be small[17]; however, the response distribution patterns of IR are known to differ from those of mail surveys and detention surveys. Some authors have stated that it is wrong to assume that only data obtained by IR deviates from the "true" rate.[17] In the present study, $Q_{non}$ was obtained from a pre-coded questionnaire. Concerning the causes of any changes in body condition that the IR subjects had experienced during the previous 3 months, the subjects were asked to select: (1) due to an ADR, (2) due to a cause not related to drugs, (3) an unexplained change in body condition that was not related to ADR, or (4) no change in body condition. The probability of selecting (3) was equivalent to $Q_{non}$. By utilizing a multiple choice answer format, the overreporting of changes in body condition due to an increased awareness of the condition, and hence, more frequent self-diagnosis cannot be ruled out. This is equivalent to the underreporting of ADR incidence data that occurs in spontaneous reports compared with that obtained in observational studies.[15] Thus, $Q_{non}$ might overestimate the "true" probability. Accordingly, this could result in $LR+Q0$ values of less than 1 for ADR with small $Q_{pre}$ values, as well as the underestimation of both $P_{post}Q+$ and $LR+Q+$.

**Future Subjects** This study focused on drug-ADR-IS combinations that the pharmacists considered clinically important. Thus, other drug-ADR-IS combinations that are encountered in clinical practice remain to be examined. It is necessary to exhaustively investigate useful IS in order to be able to predict ADR.

Ghajar *et al.* investigated the usefulness of flare as an IS for predicting sulfonamide-induced drug eruption based on the type and onset time of the flare using Bayes' theorem.[18] It is necessary to modify calculations such as ours in order to increase the probability of prevention, *e.g.*, by adding information concerning the onset time of IS. It is also necessary to investigate the usefulness of evaluating IS in consideration of the concomitant use of multiple drugs because ADR overlap and the probability of an ADR developing alters when multiple drugs are used concomitantly.[19]

## CONCLUSION

By using the AERS database, we were able to quantitatively evaluate a markedly increased number of drug-ADR-IS combinations using Bayes' theorem. As a result, it was suggested that fever, nausea, and decreased appetite are useful predictors of ADR, but pruritus and rash are less useful.

For thiamazole-induced agranulocytosis and levofloxacin- or terbinafine-induced liver disorder, fever might be a useful predictor of ADR; tremors might be useful for detecting paroxetine-induced serotonin syndrome; and decreased appetite might be a useful indicator of terbinafine-induced liver dysfunction.

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